IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

In re: Valsartan Products Liability Litigation	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge Honorable Joel Schneider, Magistrate Judge

EXHIBIT D: Copies of Websites Referenced in the Pharmacy Defendants' Memorandum of Law

/s/ Sarah E. Johnston
Sarah E. Johnston
Kara Kapke
Kristen L. Richer
BARNES & THORNBURG LLP
2029 Century Park East
Suite 300
Los Angeles, CA 90067
(310) 284-3798
(310) 284-3894

Counsel for CVS Pharmacy, Inc. (incorrectly named as CVS Health Corporation)

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TAB 1

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A206180	TABLET	ORAL	EQ 5MG BASE; 12.5MG; 160MG	AB			AUROBINDO PHARMA LTD
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A200797	TABLET	ORAL	EQ 5MG BASE; 12.5MG; 160MG	AB			LUPIN LTD
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A206180	TABLET	ORAL	EQ 5MG BASE; 25MG; 160MG	AB			AUROBINDO PHARMA LTD
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A200797	TABLET	ORAL	EQ 5MG BASE; 25MG; 160MG	AB			LUPIN LTD
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A206180	TABLET	ORAL	EQ 10MG BASE; 12.5MG; 160MG	AB			AUROBINDO PHARMA LTD
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A200797	TABLET	ORAL	EQ 10MG BASE; 12.5MG; 160MG	AB			LUPIN LTD
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A206180	TABLET	ORAL	EQ 10MG BASE; 25MG; 320MG	AB			AUROBINDO PHARMA LTD
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A206180	TABLET	ORAL	EQ 10MG BASE; 25MG; 160MG	AB			AUROBINDO PHARMA LTD
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A200797	TABLET	ORAL	EQ 10MG BASE; 25MG; 320MG	AB			LUPIN LTD
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A200797	TABLET	ORAL	EQ 10MG BASE; 25MG; 160MG	AB			LUPIN LTD
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	EXFORGE HCT	N022314	TABLET	ORAL	EQ 5MG BASE; 12.5MG; 160MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	EXFORGE HCT	N022314	TABLET	ORAL	EQ 5MG BASE; 25MG; 160MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	EXFORGE HCT	N022314	TABLET	ORAL	EQ 10MG BASE; 12.5MG; 160MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	EXFORGE HCT	N022314	TABLET	ORAL	EQ 10MG BASE; 25MG; 160MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	EXFORGE HCT	N022314	TABLET	ORAL	EQ 10MG BASE; 25MG; 320MG	AB	RLD	RS	NOVARTIS PHARMACEUTICALS CORP
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202713	TABLET	ORAL	EQ 5MG BASE; 160MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A206512	TABLET	ORAL	EQ 5MG BASE; 160MG	AB			AUROBINDO PHARMA LTD

Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A205137	TABLET	ORAL	EQ 5MG BASE; 160MG	AB			INVAGEN PHARMACEUTICALS INC
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090245	TABLET	ORAL	EQ 5MG BASE; 160MG	AB			LUPIN LTD
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090483	TABLET	ORAL	EQ 5MG BASE; 160MG	AB			MYLAN PHARMACEUTICALS INC
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202829	TABLET	ORAL	EQ 5MG BASE; 160MG	AB			NOVEL LABORATORIES INC
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202713	TABLET	ORAL	EQ 5MG BASE; 320MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A206512	TABLET	ORAL	EQ 5MG BASE; 320MG	AB			AUROBINDO PHARMA LTD
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A205137	TABLET	ORAL	EQ 5MG BASE; 320MG	AB			INVAGEN PHARMACEUTICALS INC
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090245	TABLET	ORAL	EQ 5MG BASE; 320MG	AB			LUPIN LTD
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090483	TABLET	ORAL	EQ 5MG BASE; 320MG	AB			MYLAN PHARMACEUTICALS INC
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202829	TABLET	ORAL	EQ 5MG BASE; 320MG	AB			NOVEL LABORATORIES INC
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202713	TABLET	ORAL	EQ 10MG BASE; 160MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A206512	TABLET	ORAL	EQ 10MG BASE; 160MG	AB			AUROBINDO PHARMA LTD
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A205137	TABLET	ORAL	EQ 10MG BASE; 160MG	AB			INVAGEN PHARMACEUTICALS INC
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090245	TABLET	ORAL	EQ 10MG BASE; 160MG	AB			LUPIN LTD
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090483	TABLET	ORAL	EQ 10MG BASE; 160MG	AB			MYLAN PHARMACEUTICALS INC
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202829	TABLET	ORAL	EQ 10MG BASE; 160MG	AB			NOVEL LABORATORIES INC
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202713	TABLET	ORAL	EQ 10MG BASE; 320MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A206512	TABLET	ORAL	EQ 10MG BASE; 320MG	AB			AUROBINDO PHARMA LTD
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A205137	TABLET	ORAL	EQ 10MG BASE; 320MG	AB			INVAGEN PHARMACEUTICALS INC
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090245	TABLET	ORAL	EQ 10MG BASE; 320MG	AB			LUPIN LTD
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090483	TABLET	ORAL	EQ 10MG BASE; 320MG	AB			MYLAN PHARMACEUTICALS INC
RX	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202829	TABLET	ORAL	EQ 10MG BASE; 320MG	AB			NOVEL LABORATORIES INC
RX	AMLODIPINE BESYLATE; VALSARTAN	EXFORGE	N021990	TABLET	ORAL	EQ 5MG BASE; 160MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	AMLODIPINE BESYLATE; VALSARTAN	EXFORGE	N021990	TABLET	ORAL	EQ 5MG BASE; 320MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP

Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	AMLODIPINE BESYLATE; VALSARTAN	EXFORGE	N021990	TABLET	ORAL	EQ 10MG BASE; 160MG	AB	RLD	RS	NOVARTIS PHARMACEUTICALS CORP
RX	AMLODIPINE BESYLATE; VALSARTAN	EXFORGE	N021990	TABLET	ORAL	EQ 10MG BASE; 320MG	AB	RLD	RS	NOVARTIS PHARMACEUTICALS CORP
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	DIOVAN HCT	N020818	TABLET	ORAL	12.5MG; 80MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	DIOVAN HCT	N020818	TABLET	ORAL	12.5MG; 160MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	DIOVAN HCT	N020818	TABLET	ORAL	12.5MG; 320MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	DIOVAN HCT	N020818	TABLET	ORAL	25MG; 160MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	DIOVAN HCT	N020818	TABLET	ORAL	25MG; 320MG	AB	RLD	RS	NOVARTIS PHARMACEUTICALS CORP
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A201662	TABLET	ORAL	12.5MG; 80MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A202519	TABLET	ORAL	12.5MG; 80MG	AB			AUROBINDO PHARMA LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A078946	TABLET	ORAL	12.5MG; 80MG	AB			LUPIN LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203145	TABLET	ORAL	12.5MG; 80MG	AB			MACLEODS PHARMACEUTICALS LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A078020	TABLET	ORAL	12.5MG; 80MG	AB			MYLAN PHARMACEUTICALS INC
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A206083	TABLET	ORAL	12.5MG; 80MG	AB			PRINSTON PHARMACEUTICAL INC
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A201662	TABLET	ORAL	12.5MG; 160MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A202519	TABLET	ORAL	12.5MG; 160MG	AB			AUROBINDO PHARMA LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A078946	TABLET	ORAL	12.5MG; 160MG	AB			LUPIN LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203145	TABLET	ORAL	12.5MG; 160MG	AB			MACLEODS PHARMACEUTICALS LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A078020	TABLET	ORAL	12.5MG; 160MG	AB			MYLAN PHARMACEUTICALS INC
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A206083	TABLET	ORAL	12.5MG; 160MG	AB			PRINSTON PHARMACEUTICAL INC
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A201662	TABLET	ORAL	12.5MG; 320MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A202519	TABLET	ORAL	12.5MG; 320MG	AB			AUROBINDO PHARMA LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A078946	TABLET	ORAL	12.5MG; 320MG	AB			LUPIN LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203145	TABLET	ORAL	12.5MG; 320MG	AB			MACLEODS PHARMACEUTICALS LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A078020	TABLET	ORAL	12.5MG; 320MG	AB			MYLAN PHARMACEUTICALS INC
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A206083	TABLET	ORAL	12.5MG; 320MG	AB			PRINSTON PHARMACEUTICAL INC

Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A201662	TABLET	ORAL	25MG; 160MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A202519	TABLET	ORAL	25MG; 160MG	AB			AUROBINDO PHARMA LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A078946	TABLET	ORAL	25MG; 160MG	AB			LUPIN LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203145	TABLET	ORAL	25MG; 160MG	AB			MACLEODS PHARMACEUTICALS LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A078020	TABLET	ORAL	25MG; 160MG	AB			MYLAN PHARMACEUTICALS INC
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A206083	TABLET	ORAL	25MG; 160MG	AB			PRINSTON PHARMACEUTICAL INC
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A201662	TABLET	ORAL	25MG; 320MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A202519	TABLET	ORAL	25MG; 320MG	AB			AUROBINDO PHARMA LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A078946	TABLET	ORAL	25MG; 320MG	AB			LUPIN LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203145	TABLET	ORAL	25MG; 320MG	AB			MACLEODS PHARMACEUTICALS LTD
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A078020	TABLET	ORAL	25MG; 320MG	AB			MYLAN PHARMACEUTICALS INC
RX	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A206083	TABLET	ORAL	25MG; 320MG	AB			PRINSTON PHARMACEUTICAL INC
RX	SACUBITRIL; VALSARTAN	ENTRESTO	N207620	TABLET	ORAL	24MG; 26MG		RLD		NOVARTIS PHARMACEUTICALS CORP
RX	SACUBITRIL; VALSARTAN	ENTRESTO	N207620	TABLET	ORAL	49MG; 51MG		RLD		NOVARTIS PHARMACEUTICALS CORP
RX	SACUBITRIL; VALSARTAN	ENTRESTO	N207620	TABLET	ORAL	97MG; 103MG		RLD	RS	NOVARTIS PHARMACEUTICALS CORP
RX	VALSARTAN	DIOVAN	N021283	TABLET	ORAL	40MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	VALSARTAN	DIOVAN	N021283	TABLET	ORAL	80MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	VALSARTAN	DIOVAN	N021283	TABLET	ORAL	160MG	AB	RLD		NOVARTIS PHARMACEUTICALS CORP
RX	VALSARTAN	DIOVAN	N021283	TABLET	ORAL	320MG	AB	RLD	RS	NOVARTIS PHARMACEUTICALS CORP
RX	VALSARTAN	VALSARTAN	A091367	TABLET	ORAL	40MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A205536	TABLET	ORAL	40MG	AB			ALKEM LABORATORIES LTD
RX	VALSARTAN	VALSARTAN	A204011	TABLET	ORAL	40MG	AB			AMNEAL PHARMACEUTICALS OF NEW YORK LLC
RX	VALSARTAN	VALSARTAN	A202223	TABLET	ORAL	40MG	AB			AUROBINDO PHARMA LTD
RX	VALSARTAN	VALSARTAN	A203311	TABLET	ORAL	40MG	AB			HETERO LABS LTD UNIT V
RX	VALSARTAN	VALSARTAN	A077530	TABLET	ORAL	40MG	AB			IVAX PHARMACEUTICALS INC
RX	VALSARTAN	VALSARTAN	A203536	TABLET	ORAL	40MG	AB			JUBILANT GENERICS LTD
RX	VALSARTAN	VALSARTAN	A201677	TABLET	ORAL	40MG	AB			LUPIN LTD

Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	VALSARTAN	VALSARTAN	A202696	TABLET	ORAL	40MG	AB			MACLEODS PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A090866	TABLET	ORAL	40MG	AB			MYLAN PHARMACEUTICALS INC
RX	VALSARTAN	VALSARTAN	A077492	TABLET	ORAL	40MG	AB			OHM LABORATORIES INC
RX	VALSARTAN	VALSARTAN	A204821	TABLET	ORAL	40MG	AB			PRINSTON PHARMACEUTICAL INC
RX	VALSARTAN	VALSARTAN	A205347	TABLET	ORAL	40MG	AB			SQUARE PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A209261	TABLET	ORAL	40MG	AB			UNICHEM LABORATORIES LTD
RX	VALSARTAN	VALSARTAN	A091367	TABLET	ORAL	80MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A205536	TABLET	ORAL	80MG	AB			ALKEM LABORATORIES LTD
RX	VALSARTAN	VALSARTAN	A204011	TABLET	ORAL	80MG	AB			AMNEAL PHARMACEUTICALS OF NEW YORK LLC
RX	VALSARTAN	VALSARTAN	A202223	TABLET	ORAL	80MG	AB			AUROBINDO PHARMA LTD
RX	VALSARTAN	VALSARTAN	A203311	TABLET	ORAL	80MG	AB			HETERO LABS LTD UNIT V
RX	VALSARTAN	VALSARTAN	A077530	TABLET	ORAL	80MG	AB			IVAX PHARMACEUTICALS INC
RX	VALSARTAN	VALSARTAN	A203536	TABLET	ORAL	80MG	AB			JUBILANT GENERICS LTD
RX	VALSARTAN	VALSARTAN	A201677	TABLET	ORAL	80MG	AB			LUPIN LTD
RX	VALSARTAN	VALSARTAN	A202696	TABLET	ORAL	80MG	AB			MACLEODS PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A090866	TABLET	ORAL	80MG	AB			MYLAN PHARMACEUTICALS INC
RX	VALSARTAN	VALSARTAN	A077492	TABLET	ORAL	80MG	AB			OHM LABORATORIES INC
RX	VALSARTAN	VALSARTAN	A204821	TABLET	ORAL	80MG	AB			PRINSTON PHARMACEUTICAL INC
RX	VALSARTAN	VALSARTAN	A205347	TABLET	ORAL	80MG	AB			SQUARE PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A209261	TABLET	ORAL	80MG	AB			UNICHEM LABORATORIES LTD
RX	VALSARTAN	VALSARTAN	A091367	TABLET	ORAL	160MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A205536	TABLET	ORAL	160MG	AB			ALKEM LABORATORIES LTD
RX	VALSARTAN	VALSARTAN	A204011	TABLET	ORAL	160MG	AB			AMNEAL PHARMACEUTICALS OF NEW YORK LLC
RX	VALSARTAN	VALSARTAN	A202223	TABLET	ORAL	160MG	AB			AUROBINDO PHARMA LTD
RX	VALSARTAN	VALSARTAN	A203311	TABLET	ORAL	160MG	AB			HETERO LABS LTD UNIT V
RX	VALSARTAN	VALSARTAN	A077530	TABLET	ORAL	160MG	AB			IVAX PHARMACEUTICALS INC
RX	VALSARTAN	VALSARTAN	A203536	TABLET	ORAL	160MG	AB			JUBILANT GENERICS LTD
RX	VALSARTAN	VALSARTAN	A201677	TABLET	ORAL	160MG	AB			LUPIN LTD

Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	VALSARTAN	VALSARTAN	A202696	TABLET	ORAL	160MG	AB			MACLEODS PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A090866	TABLET	ORAL	160MG	AB			MYLAN PHARMACEUTICALS INC
RX	VALSARTAN	VALSARTAN	A077492	TABLET	ORAL	160MG	AB			OHM LABORATORIES INC
RX	VALSARTAN	VALSARTAN	A204821	TABLET	ORAL	160MG	AB			PRINSTON PHARMACEUTICAL INC
RX	VALSARTAN	VALSARTAN	A205347	TABLET	ORAL	160MG	AB			SQUARE PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A209261	TABLET	ORAL	160MG	AB			UNICHEM LABORATORIES LTD
RX	VALSARTAN	VALSARTAN	A091367	TABLET	ORAL	320MG	AB			ALEMBIC PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A205536	TABLET	ORAL	320MG	AB			ALKEM LABORATORIES LTD
RX	VALSARTAN	VALSARTAN	A204011	TABLET	ORAL	320MG	AB			AMNEAL PHARMACEUTICALS OF NEW YORK LLC
RX	VALSARTAN	VALSARTAN	A202223	TABLET	ORAL	320MG	AB			AUROBINDO PHARMA LTD
RX	VALSARTAN	VALSARTAN	A203311	TABLET	ORAL	320MG	AB			HETERO LABS LTD UNIT V
RX	VALSARTAN	VALSARTAN	A077530	TABLET	ORAL	320MG	AB			IVAX PHARMACEUTICALS INC
RX	VALSARTAN	VALSARTAN	A203536	TABLET	ORAL	320MG	AB			JUBILANT GENERICS LTD
RX	VALSARTAN	VALSARTAN	A201677	TABLET	ORAL	320MG	AB			LUPIN LTD
RX	VALSARTAN	VALSARTAN	A202696	TABLET	ORAL	320MG	AB			MACLEODS PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A090866	TABLET	ORAL	320MG	AB			MYLAN PHARMACEUTICALS INC
RX	VALSARTAN	VALSARTAN	A077492	TABLET	ORAL	320MG	AB			OHM LABORATORIES INC
RX	VALSARTAN	VALSARTAN	A204821	TABLET	ORAL	320MG	AB			PRINSTON PHARMACEUTICAL INC
RX	VALSARTAN	VALSARTAN	A205347	TABLET	ORAL	320MG	AB			SQUARE PHARMACEUTICALS LTD
RX	VALSARTAN	VALSARTAN	A209261	TABLET	ORAL	320MG	AB			UNICHEM LABORATORIES LTD
DISCN	ALISKIREN HEMIFUMARATE; VALSARTAN	VALTURNA	N022217	TABLET	ORAL	EQ 150MG BASE; 160MG				NOVARTIS PHARMACEUTICALS CORP
DISCN	ALISKIREN HEMIFUMARATE; VALSARTAN	VALTURNA	N022217	TABLET	ORAL	EQ 300MG BASE; 320MG				NOVARTIS PHARMACEUTICALS CORP
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A201087	TABLET	ORAL	EQ 5MG BASE; 12.5MG; 160MG				PAR PHARMACEUTICAL INC
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A200435	TABLET	ORAL	EQ 5MG BASE; 12.5MG; 160MG				TEVA PHARMACEUTICALS USA
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A201593	TABLET	ORAL	EQ 5MG BASE; 12.5MG; 160MG				TORRENT PHARMACEUTICALS LTD

Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A201087	TABLET	ORAL	EQ 5MG BASE; 25MG; 160MG				PAR PHARMACEUTICAL INC
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A200435	TABLET	ORAL	EQ 5MG BASE; 25MG; 160MG				TEVA PHARMACEUTICALS USA
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A201593	TABLET	ORAL	EQ 5MG BASE; 25MG; 160MG				TORRENT PHARMACEUTICALS LTD
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A201087	TABLET	ORAL	EQ 10MG BASE; 12.5MG; 160MG				PAR PHARMACEUTICAL INC
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A200435	TABLET	ORAL	EQ 10MG BASE; 12.5MG; 160MG				TEVA PHARMACEUTICALS USA
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A201593	TABLET	ORAL	EQ 10MG BASE; 12.5MG; 160MG				TORRENT PHARMACEUTICALS LTD
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A201087	TABLET	ORAL	EQ 10MG BASE; 25MG; 160MG				PAR PHARMACEUTICAL INC
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A201087	TABLET	ORAL	EQ 10MG BASE; 25MG; 320MG				PAR PHARMACEUTICAL INC
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A200435	TABLET	ORAL	EQ 10MG BASE; 25MG; 160MG				TEVA PHARMACEUTICALS USA
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A200435	TABLET	ORAL	EQ 10MG BASE; 25MG; 320MG				TEVA PHARMACEUTICALS USA
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A201593	TABLET	ORAL	EQ 10MG BASE; 25MG; 160MG				TORRENT PHARMACEUTICALS LTD
DISCN	AMLODIPINE BESYLATE; HYDROCHLOROTHIAZIDE; VALSARTAN	AMLODIPINE BESYLATE, VALSARTAN AND HYDROCHLOROTHIAZIDE	A201593	TABLET	ORAL	EQ 10MG BASE; 25MG; 320MG				TORRENT PHARMACEUTICALS LTD
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090011	TABLET	ORAL	EQ 5MG BASE; 160MG				PAR PHARMACEUTICAL INC
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A091235	TABLET	ORAL	EQ 5MG BASE; 160MG				TEVA PHARMACEUTICALS USA
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202377	TABLET	ORAL	EQ 5MG BASE; 160MG				TORRENT PHARMACEUTICALS LTD
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090011	TABLET	ORAL	EQ 5MG BASE; 320MG				PAR PHARMACEUTICAL INC
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A091235	TABLET	ORAL	EQ 5MG BASE; 320MG				TEVA PHARMACEUTICALS USA
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202377	TABLET	ORAL	EQ 5MG BASE; 320MG				TORRENT PHARMACEUTICALS LTD
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090011	TABLET	ORAL	EQ 10MG BASE; 160MG				PAR PHARMACEUTICAL INC
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A091235	TABLET	ORAL	EQ 10MG BASE; 160MG				TEVA PHARMACEUTICALS USA

Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202377	TABLET	ORAL	EQ 10MG BASE; 160MG				TORRENT PHARMACEUTICALS LTD
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A090011	TABLET	ORAL	EQ 10MG BASE; 320MG				PAR PHARMACEUTICAL INC
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A091235	TABLET	ORAL	EQ 10MG BASE; 320MG				TEVA PHARMACEUTICALS USA
DISCN	AMLODIPINE BESYLATE; VALSARTAN	AMLODIPINE BESYLATE AND VALSARTAN	A202377	TABLET	ORAL	EQ 10MG BASE; 320MG				TORRENT PHARMACEUTICALS LTD
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203026	TABLET	ORAL	12.5MG; 80MG				APOTEX INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A091519	TABLET	ORAL	12.5MG; 80MG				WATSON LABORATORIES INC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203000	TABLET	ORAL	12.5MG; 80MG				ZYDUS PHARMACEUTICALS USA INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203026	TABLET	ORAL	12.5MG; 160MG				APOTEX INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A091519	TABLET	ORAL	12.5MG; 160MG				WATSON LABORATORIES INC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203000	TABLET	ORAL	12.5MG; 160MG				ZYDUS PHARMACEUTICALS USA INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203026	TABLET	ORAL	12.5MG; 320MG				APOTEX INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A091519	TABLET	ORAL	12.5MG; 320MG				WATSON LABORATORIES INC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203000	TABLET	ORAL	12.5MG; 320MG				ZYDUS PHARMACEUTICALS USA INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203026	TABLET	ORAL	25MG; 160MG				APOTEX INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A091519	TABLET	ORAL	25MG; 160MG				WATSON LABORATORIES INC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203000	TABLET	ORAL	25MG; 160MG				ZYDUS PHARMACEUTICALS USA INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203026	TABLET	ORAL	25MG; 320MG				APOTEX INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A091519	TABLET	ORAL	25MG; 320MG				WATSON LABORATORIES INC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
DISCN	HYDROCHLOROTHIAZIDE; VALSARTAN	VALSARTAN AND HYDROCHLOROTHIAZIDE	A203000	TABLET	ORAL	25MG; 320MG				ZYDUS PHARMACEUTICALS USA INC
DISCN	NEBIVOLOL HYDROCHLORIDE; VALSARTAN	BYVALSON	N206302	TABLET	ORAL	EQ 5MG BASE; 80MG		RLD		ALLERGAN SALES LLC

Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
DISCN	VALSARTAN	DIOVAN	N020665	CAPSULE	ORAL	80MG				NOVARTIS PHARMACEUTICALS CORP
DISCN	VALSARTAN	DIOVAN	N020665	CAPSULE	ORAL	160MG				NOVARTIS PHARMACEUTICALS CORP
DISCN	VALSARTAN	PREXXARTAN	N209139	SOLUTION	ORAL	20MG/5ML		RLD		CARMEL BIOSCIENCES INC
DISCN	VALSARTAN	PREXXARTAN	N209139	SOLUTION	ORAL	80MG/20ML		RLD		CARMEL BIOSCIENCES INC
DISCN	VALSARTAN	VALSARTAN	A202728	TABLET	ORAL	40MG				TORRENT PHARMACEUTICALS LTD
DISCN	VALSARTAN	VALSARTAN	A090642	TABLET	ORAL	40MG				WATSON LABORATORIES INC
DISCN	VALSARTAN	VALSARTAN	A202728	TABLET	ORAL	80MG				TORRENT PHARMACEUTICALS LTD
DISCN	VALSARTAN	VALSARTAN	A090642	TABLET	ORAL	80MG				WATSON LABORATORIES INC
DISCN	VALSARTAN	VALSARTAN	A202728	TABLET	ORAL	160MG				TORRENT PHARMACEUTICALS LTD
DISCN	VALSARTAN	VALSARTAN	A090642	TABLET	ORAL	160MG				WATSON LABORATORIES INC
DISCN	VALSARTAN	VALSARTAN	A202728	TABLET	ORAL	320MG				TORRENT PHARMACEUTICALS LTD
DISCN	VALSARTAN	VALSARTAN	A090642	TABLET	ORAL	320MG				WATSON LABORATORIES INC

TAB 2

FDA NEWS RELEASE

FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity

For Immediate Release:

July 13, 2018

For additional information related to valsartan, please visit: FDA updates on valsartan recalls (/drugs/drug-safety-and-availability/fda-updates-valsartan-recalls)

This press release was updated on July 17, 2018, to add links to the press releases issued by each company, to include information about supplier of the active ingredient and to update the contact information for consumers.

Español (/news-events/comunicados-de-prensa/la-fda-anuncia-el-retiro-voluntario-del-mercado-de-varios-medicamentos-que-contienen-valsartan-tras)

The U.S. Food and Drug Administration is alerting health care professionals and patients of a voluntary recall of several drug products containing the active ingredient valsartan, used to treat high blood pressure and heart failure. This recall is due to an impurity, N-nitrosodimethylamine (NDMA), which was found in the recalled products. However, not all products containing valsartan are being recalled. NDMA is classified as a probable human carcinogen (a substance that could cause cancer) based on results from laboratory tests. The presence of NDMA was unexpected and is thought to be related to changes in the way the active substance was manufactured.

The FDA's review is ongoing and has included investigating the levels of NDMA in the recalled products, assessing the possible effect on patients who have been taking them and what measures can be taken to reduce or eliminate the impurity from future batches produced by the company.

"The FDA is committed to maintaining our gold standard for safety and efficacy. That includes our efforts to ensure the quality of drugs and the safe manner in which they're manufactured," said FDA Commissioner Scott Gottlieb, M.D. "When we identify lapses in the quality of drugs and problems with their manufacturing that have the potential to create risks to patients, we're committed to taking swift action to alert the public and help facilitate the removal of the products from the market. As we seek the removal of certain drug products today, our drug shortages team is also working hard to ensure patients' therapeutic needs are met in the United States with an adequate supply of unaffected medications."

Information for Patients and Health Care Professionals

- Because valsartan is used in medicines to treat serious medical conditions, patients taking the recalled valsartan-containing medicines should continue taking their medicine until they have a replacement product.
- To determine whether a specific product has been recalled, patients should look at the drug name and company name on the label of their prescription bottle. If the information is not on the bottle, patients should contact the pharmacy that dispensed the medicine.
- If a patient is taking one of the recalled medicines listed below, they should follow the recall instructions provided by the specific company. This information will be posted to the FDA's website (/drug-recalls).

- Patients should also contact their health care professional (the pharmacist who dispensed the medication or doctor who prescribed the medication) if their medicine is included in this recall to discuss their treatment, which may include another valsartan product not affected by this recall or an alternative treatment option.

The companies listed below are recalling all lots of non-expired products that contain the ingredient valsartan supplied to them by Zhejiang Huahai Pharmaceuticals, Linhai, China. Not all valsartan-containing medicines distributed in the United States have valsartan active pharmaceutical ingredient (API) supplied by this specific company. Zhejiang Huahai has stopped distributing its valsartan API and the FDA is working with the affected companies to reduce or eliminate the valsartan API impurity from future products.

Recalled Products

Medicine	Company
Valsartan	Major Pharmaceuticals (/safety/recalls-market-withdrawals-safety-alerts/major-pharmaceuticals-issues-voluntary-nationwide-recall-valsartan-due-potential-presence-probable)
Valsartan	Solco Healthcare (/safety/recalls-market-withdrawals-safety-alerts/prinston-pharmaceutical-inc-issues-voluntary-nationwide-recall-valsartan-and-valsartan-hctz-tablets)
Valsartan	Teva Pharmaceuticals Industries Ltd. (/safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-issues-voluntary-nationwide-recall-valsartan-and-valsartan)
Valsartan/Hydrochlorothiazide (HCTZ)	Solco Healthcare (/safety/recalls-market-withdrawals-safety-alerts/prinston-pharmaceutical-inc-issues-voluntary-nationwide-recall-valsartan-and-valsartan-hctz-tablets)
Valsartan/Hydrochlorothiazide (HCTZ)	Teva Pharmaceuticals Industries Ltd. (/safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-issues-voluntary-nationwide-recall-valsartan-and-valsartan)

“We have carefully assessed the valsartan-containing medications sold in the United States, and we’ve found that the valsartan sold by these specific companies does not meet our safety standards. This is why we’ve asked these companies to take immediate action to protect patients,” said Janet Woodcock, M.D., director of the FDA’s Center for Drug Evaluation and Research.

The FDA will continue to investigate this issue and provide additional information when it becomes available. The agency encourages patients and health care professionals to report any adverse reaction to the FDA’s MedWatch program (/medwatch-fda-safety-information-and-adverse-event-reporting-program).

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation’s food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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Inquiries

Media:

Sandy Walsh (mailto:sandy.walsh@fda.hhs.gov)

301-796-4669

Consumer:

888-INFO-FDA

Related Information

- FDA updates health care professionals and patients on recent valsartan recalls (/drugs/drug-safety-and-availability/fda-updates-valsartan-recalls)

More Press Announcements (/news-events/newsroom/press-announcements)

TAB 3

David Light
Kaury Kucera, PhD
Valisure, LLC
5 Science Park
New Haven, CT 06511

April 1, 2020

Re: Docket No. FDA-2019-P-4281

Dear Mr. Light and Dr. Kucera:

This letter responds to your citizen petition submitted on behalf of Valisure LLC and ValisureRX, LLC (collectively referred to as Valisure), received on September 13, 2019 (Petition). The Petition requests that the Food and Drug Administration (FDA or the Agency) take the following actions based on Valisure's testing and detection of high levels of N-Nitrosodimethylamine (NDMA) in specific lots of ranitidine hydrochloride (ranitidine), sold under the brand name Zantac:[1]

(1) Request a recall and suspend sale of all lots of all products containing ranitidine;

(2) Conduct examinations and investigation under section 702(a) of the FD&C Act (21 U.S.C. 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for approval under section 704(a) of the FD&C Act (21 U.S.C. 374(a));

(3) Provide information to the public regarding these products under section 705(b) of the FD&C Act (21 U.S.C. 375(b));

(4) In addition to the instructions for disposal and/or return in the recall notices, issue additional guidance to the public for the safe disposal of ranitidine, given the recognized potential that the drug may degrade to form the probable carcinogen NDMA in municipal wastewater treatment plants and impact the public water supply; and

(5) Promulgate regulations requiring robust independent chemical testing and verification of pharmaceuticals and, while these regulations are pending, issue guidance requesting such testing and verification.

[1] Ranitidine hydrochloride is available in many dosage forms, including tablets, capsules, injections, and syrups, and is available under the brand name Zantac, as well as under the generic name of the active ingredient, ranitidine hydrochloride. We limit this response to ranitidine hydrochloride, although the substance of the response may be relevant to other drug products such as nizatidine, which is mentioned in the Petition.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Petition at 2.

We have carefully considered your Petition and other information available to the Agency. For the reasons stated below, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Ranitidine

Ranitidine is an acid reducer that is available in prescription and over-the-counter (OTC) drug products. It is a histamine-2 (H2) blocker, which decreases the amount of acid created by the stomach. OTC ranitidine products are approved to prevent and relieve heartburn associated with acid indigestion and sour stomach. Prescription ranitidine products are approved for multiple indications, including treatment and prevention of ulcers of the stomach and intestines and treatment of gastroesophageal reflux disease. The first ranitidine product, which had the brand name Zantac, was approved in 1985 and has been marketed in the United States since that time.

B. N-Nitrosodimethylamine

NDMA is a semivolatile organic chemical that forms in both industrial and natural processes.[2] It is not currently produced or commercially used in the United States, but may be unintentionally produced in and released from industrial sources through chemical reactions, such as those that involve alkylamines with nitrogen oxides, nitrous acid, or nitrate salts.[3] It can also be inadvertently formed in air, water, and soil from reactions to alkylamines, which are found widely distributed throughout the environment.[4]

NDMA exposure may occur through ingesting foods that contain nitrosamines,[5] such as smoked or cured meats and fish, ingesting food that contains alkylamines (which can cause NDMA to form in the stomach), drinking contaminated water, drinking malt beverages (such as beer and whiskey) that may contain low levels of nitrosamines formed during processing, using toilet and

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[2] See the United States Environmental Protection Agency's (EPA) November 2017 "Technical Fact Sheet—NDMA" (EPA Fact Sheet), available at https://www.epa.gov/sites/production/files/2017-10/documents/ndma_fact_sheet_update_9-15-17_508.pdf.

[3] Id.

[4] See the *Toxicological Profile for N-Nitrosodimethylamine* at 1, (December 1989), available through the Agency for Toxic Substances and Disease Registry's (ATSDR) web page, "Toxic Substances Portal - N-nitrosodimethylamine" at https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=884&tid=173.

[5] In general, the term *nitrosamine* is used to describe the chemical class of organic compounds that have a certain chemical structure and are expected to react in predictable and similar ways when other chemical compounds come in contact with them. Nitrosamines, as opposed to the individual NDMA impurity, became important in FDA's evaluation of angiotensin II receptor blockers (ARBs), because more than one impurity was discovered in some of those medications. This has not been the case with ranitidine.

cosmetic products such as shampoos and cleansers that contain NDMA, and breathing or inhaling cigarette smoke.[6] The oral route, in consumption of contaminated food and water, is the primary human exposure pathway for NDMA.[7]

NDMA has been classified as a probable carcinogen by the International Agency for Research on Cancer (IARC).[8] Based on its review, IARC concluded that there was sufficient evidence of a carcinogenic effect of NDMA in many experimental animals, and that despite the lack of epidemiological data, NDMA should be regarded for practical purposes as if it were carcinogenic to humans.[9] The 1987 IARC update for carcinogenic classification identifies NDMA as "Group 2A: Probably carcinogenic to humans."[10]

C. Legal Framework for Recalls, Market Withdrawals, Investigations, and Disclosure of Information to the Public

Drug applicants must ensure that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of drugs are adequate to assure and preserve identity, strength, quality, and purity.[11] FDA continues to review the quality of drug products throughout the life cycle of the products, and may take regulatory action to facilitate the voluntary recall of a drug product when the Agency determines that a product in the market violates provisions of the FD&C Act or presents a danger to health.[12] The introduction or delivery for introduction into

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[6] EPA Fact Sheet at 3.

[7] Id., citing ATSDR toxicological profile for NDMA.

[8] See original IARC review, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemical to Man, Vol. 1 (1972) NDMA at 95; IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Vols. 1 to 42 (1987); Supp 7, NDMA at 67; and see generally IARC Monographs on the Identification of Carcinogenic Hazards to Humans, Amended Preamble, January 2019.

[9] See IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Some N-Nitro Compounds, Vol. 17 (1978) at 152.

[10] IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Vols. 1 to 42 (1987) at 42. This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. Exceptionally, an agent may be classified into this category solely on the basis of *limited evidence* of carcinogenicity in humans or of *sufficient evidence* of carcinogenicity in experimental animals strengthened by supporting evidence from other relevant data. Id. at 31.

[11] See section 505(e) of the FD&C Act, 21 U.S.C. 355(e), section 505(j)(4)(A) of the FD&C Act, 21 U.S.C. 355(j)(4)(A).

[12] See 21 CFR 7.40(a); see also the FDA draft guidance for industry and FDA staff *Initiation of Voluntary Recalls under 21 CFR Part 7, Subpart C* (April 2019), at 9. FDA is committed to working cooperatively with a recalling firm whenever possible to facilitate the orderly and prompt removal of, or correction to, a violative product in the marketplace, particularly when the product presents a danger to health. When final, this guidance will represent

interstate commerce of any drug that is adulterated[13] or misbranded[14] is a violation of section 301(a) of the FD&C Act (21 U.S.C. 331(a)).

A recall is a firm's removal or correction of a marketed product that FDA considers to be in violation of the laws it administers.[15] It is an effective method of removing or correcting defective FDA-regulated products that have been distributed commercially, particularly when those products present a danger to health.[16] It is generally a voluntary action by manufacturers and distributors to protect the public health from products that present a risk of injury.[17] A recall may be undertaken voluntarily at any time by manufacturers and distributors, or initiated at the request of FDA when there is an urgent situation.[18] FDA generally directs a recall request to the firm that has primary responsibility for the manufacture and marketing of the product.[19] A recall is generally more appropriate and affords better protection for consumers than seizure, which

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FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[13] Section 501(a)(2)(B) of the FD&C Act establishes that a drug is deemed to be adulterated if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess" (21 U.S.C. 351(a)(2)(B)). Under section 501 of the FD&C Act, "current good manufacturing practice" (CGMP) includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products (21 U.S.C. 351). The Agency has promulgated regulations at 21 CFR parts 210 and 211 concerning CGMP requirements for drugs. A drug that does not satisfy the requirements of the FD&C Act or the Agency's CGMP regulations is deemed to be adulterated. Section 501(a)(2(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(b).

[14] Under 502(j) of the FD&C Act, a drug shall be deemed to be misbranded "[i]f it is dangerous to health when used in the dosage or manner; or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof." (21 U.S.C. 352(j)). Under section 201(n) and 502(a)(1) of the FD&C Act, a drug may be deemed to be misbranded if the labeling fails to reveal a material fact that the drug contains, or could contain, if stored under normal storage conditions, a dangerous ingredient. (21 U.S.C. 321(n) and 21 U.S.C.352(a)(1)).

[15] 21 CFR 7.3(g).

[16] 21 CFR 7.40(a); Preamble to Final Rule, 43 FR 26202 (June 16, 1978).

[17] Id.; see also FDA draft guidance *Initiation of Voluntary Recalls Under 21 CFR Part 7, Subpart C* (April 2019) and the FDA guidance *Public Warning and Notification of Recalls Under 21 CFR Part 7, Subpart C* (February 2019). With limited exceptions not applicable here, FDA does not have authority under the FD&C Act to order a firm to recall a violative drug product.

[18] 21 CFR 7.40(b), 21 CFR 7.45, 21 CFR 7.46; see also FDA draft guidance *Initiation of Voluntary Recalls under 21 CFR Part 7, Subpart C* (April 2019). Section 7.45(a) specifically addresses FDA requested recalls, and states that the Agency may request a firm to initiate a recall when the following determinations have been made: 1) that a product that has been distributed presents a risk of illness or injury or gross consumer deception; 2) that the firm has not initiated a recall of the product; and 3) that an agency action is necessary to protect the public health and welfare.

[19] 21 CFR 7.40(b).

requires legal action and a court order, particularly when many lots of product have been widely distributed.[20] As described in guidance, firms in a product distribution chain should be "recall ready" to help minimize public exposure to products in violation of the FD&C Act and other laws administered by FDA.[21] The Agency will work with manufacturers and distributors to develop a recall strategy and to publicize information to the public. FDA will monitor the effectiveness of any recall and take additional action as appropriate.

FDA's regulations also provide a procedure for product removal, which is called a *market withdrawal*, when a firm's removal or correction of a distributed product may not be immediately subject to legal action by FDA.[22,23] Similar to a recall, FDA will request that a firm implement a request for a market withdrawal of a specific drug product. When completed, a market withdrawal will effectively remove all of an identified product from the market. Additionally, the Agency has procedures in place under which it can monitor and oversee the effectiveness of the actions taken by manufacturers and applicants to complete the market withdrawal.[24]

Under section 704(a)(4)(A) of the FD&C Act, FDA may conduct factory inspections to obtain records from an establishment engaged in the manufacture, preparation, propagation, compounding or processing of a drug in advance or in lieu of an inspection.[25] Section 704(a)(1) of the FD&C Act broadly defines factory, warehouse or establishment inspections to include such facilities where prescription drugs or nonprescription drugs are manufactured, processed, packed or held, and include inspection of records, files, papers processes, controls and facilities.[26] Further, FDA may request and evaluate information from applicants and

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[20] 21 CFR 7.40(c).

[21] See the FDA draft guidance *Initiation of Voluntary Recalls* (April 2019) at 3 (identify and train appropriate personnel, establish a recall communications plan, identify reporting requirements, use adequate product coding and maintain distribution records). The regulations are intended to guide industry on how it should prepare for a recall and suggests that records should be retained for a period of time that exceeds the shelf life and expected use of the product and is at least the time specified in the regulations concerning records retention. 21 CFR 7.59(c). FDA's guidance provides further information to industry recommending that distribution records should include enough detail to identify the consignees that actually received the recalled product and should conform to any applicable requirements. It also recommends that direct accounts that further distribute the product should also maintain records of their consignees that actually received the product, to ensure the recalling firm's instructions are extended to all consignees in the distribution chain (see the draft guidance *Initiation of Voluntary Recalls* at 5).

[22] 21 CFR 7.3(j).

[23] A market withdrawal as defined by 21 CFR 7.3(j) differs from the procedure for withdrawal of an application as described in our regulations at 21 CFR 314.150. As used in this response, the term *withdrawal* is meant to refer to market withdrawal under § 7.3(j) and not application withdrawal under § 314.150.

[24] See FDA Regulatory Procedures Manual, Chapter 7: Recall Procedures (Version 6) at 6 and 9 (Similar to a recall, a product withdrawal recommendation can be entered into FDA's data system to allow the Agency to document and monitor the market withdrawal).

[25] 21 U.S.C. 374(a)(4)(A).

[26] 21 U.S.C. 374(a)(1).

manufacturers to ensure that an approved drug product continues to be safe and effective, and to ensure that drug products meet applicable standards under CGMP[27] and are not adulterated.[28]

An important priority for FDA is to disclose information to the public on drugs that may harm the public health. The recall regulations specifically address the need for FDA to issue public warnings when there is a company-initiated or FDA recommended recall of a product under 21 CFR part 7, subpart C.[29] 21 C.F.R. 7.42(b)(2). The purpose of a public warning under this section is to alert the public that a product being recalled presents a serious health risk. FDA may issue public warnings in a variety of forms, including but not limited to press release, emails, and web and social media postings.[30] Id. It is important that a public warning be distributed in a way that ensures that the information conveyed in the warning actually reaches the public. While regulations and guidance on communications typically refer to recalls, it is FDA's policy to provide similar, appropriate public warnings and communications regarding the market withdrawal of a product.[31]

II. SUMMARY OF FDA ACTIONS REGARDING RANITIDINE DRUG PRODUCTS

FDA issued its first public statement on ranitidine on September 13, 2019, when the Agency alerted patients and healthcare professionals that it had learned that some ranitidine drug products had NDMA impurities at low levels.[32] The Agency stated that it would investigate this

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[27] 21 CFR parts 210 and 211; see e.g., 21 CFR 210.1(b) (the failure to comply with any regulation set forth in this part and in parts 211, 225, and 226 of this chapter in the manufacture, processing, packing or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the FD&C Act); 21 CFR 211.80(b) (requiring manufacturers to handle and store active ingredients and other drug product components, among other things, in a manner to prevent contamination); 211.160(b) (requiring manufacturers to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that active ingredients and other drug product components, among other things, conform to appropriate standards of identity, strength, quality, and purity); 211.166 (requiring a written testing program to assess the stability characteristics of drug products, which will be used in determining appropriate storage conditions and expiration dates).

[28] See footnote 13.

[29] See FDA guidance for industry *Public Warning and Notification of Recalls Under 21 CFR Part 7, Subpart C* (February 2019).

[30] Id. at 5 and 10.

[31] See footnote 24; FDA's web page FDA 101: Product Recalls, available at https://www.fda.gov/consumers/consumer-updates/fda-101-product-recalls; and FDA guidance on Product Recalls, Including Removals and Corrections (November 2003) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-recalls-including-removals-and-corrections.

[32] FDA created a website to inform the public of its investigation and recommendations, see FDA Updates and Press Announcements on NDMA in Zantac (ranitidine), available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine (Ranitidine web page). FDA's laboratory began testing a small number of ranitidine products for the presence of NDMA. Because the preliminary results found all of the samples were positive for NDMA at low levels, the Agency began a thorough investigation of the levels of NDMA in ranitidine.

concern and would keep the public informed. Shortly thereafter, FDA announced that a manufacturer was voluntarily recalling certain lots of prescription ranitidine because NDMA was found to be above limits established by FDA. At that time, FDA scientists also published an appropriate testing protocol that could be used to detect NDMA impurities in ranitidine.[33] Subsequently, on September 26, 2019, FDA alerted patients and healthcare professionals on its webpage that certain retailers would be voluntarily recalling OTC ranitidine products sold under their labels and produced by a certain manufacturer because the medicines may contain low levels of NDMA.[34]

Both FDA and industry reacted quickly to sampling data that indicated NDMA impurities might be present in ranitidine because of information and data collection from the on-going investigation of nitrosamine impurities in angiotensin II receptor blockers (ARBs).[35] However, it was important to obtain NDMA impurity information on ranitidine to see how frequently it appeared and at what levels, and to research and determine the potential root causes of the impurity in these drug products. In October 2019, FDA sent information request letters to all ranitidine active drug master file (DMF)[36] and application holders asking them to assess their processes for nitrosamine formation risk and to test recent batches of drug substance and drug product for NDMA. If NDMA was found, the firms were asked to provide FDA a summary of their root cause analysis. FDA also asked specific companies to send samples of ranitidine drug product and drug substance to FDA to be tested by our scientists.

Also during October 2019, some application holders initiated additional voluntary recalls that were included on FDA's Ranitidine webpage. By the end of the month, FDA concluded it had

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[33] The test method identified and posted on FDA's Ranitidine web page is appropriate for testing nitrosamines, the class of chemical compounds to which NDMA belongs. FDA decided to publish this appropriate test method, and subsequently published an alternative test method, because it found that some types of test methods themselves created the impurity that was being tested. Specifically, the test method FDA had previously posted for testing angiotensin II receptor blockers (ARBs) for nitrosamines was not appropriate for use in testing NDMA in ranitidine (see FDA's 10/2/2019 update; FDA's 10/23/2019 update includes second test method).

[34] See Ranitidine web page identified in footnote 32. FDA conducted a health hazard evaluation (HHE) as required under section 7.41 of the recall regulations (21 CFR 7.41). Based on the HHE, FDA determined that the recall would be assigned to a classification of II, which is defined as "a product that might cause a temporary health problem, or pose a slight threat of a serious nature." See FDA's web page FDA 101: Product Recalls discussing recall classifications, available at https://www.fda.gov/consumers/consumer-updates/fda-101-product-recalls.

[35] See FDA's web page FDA Updates and Press Announcements on angiotensin II receptor blockers (ARBs), (Valsartan, Losartan and Irbesartan), available at https://www.fda.gov/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan.

[36] A drug master file (DMF) contains information that FDA may use to permit the holder to incorporate the information by reference when the holder submits an application, or to permit the holder to authorize other persons to rely on the information to support a submission to FDA without the holder having to disclose the information to the person. 21 CFR 314.420(a). A DMF may include information about: the drug substance, drug substance intermediate, and materials used in their preparation, or drug product; packaging materials; excipient, colorant, flavor, essence, or materials used in their preparation (21 CFR 314.420(a)(2), (3) and (4)).

sufficient information to recommend to manufacturers that they voluntarily recall ranitidine if either their testing, or FDA's testing of their products, indicated that the NDMA level was above an acceptable daily intake (ADI) concentration of 0.32 parts per million (ppm) or 96 nanograms (ng)/day.[37] FDA sent additional information requests to inform application holders and DMF holders that a limit had been set for this impurity and to ask for additional information.

A summary of this information was published on the FDA Ranitidine web page on November 1, 2019. It informed the public that FDA was asking companies to continue to test their products and the Agency was continuing to work with manufacturers to understand the root cause of the low levels of NDMA in these drug products. The Agency published a second document that contained a summary of the results FDA had obtained on NDMA testing in ranitidine products.[38] Since September 2019, overall, the Office of Testing and Research (OTR) in FDA's Office of Pharmaceutical Quality has tested approximately 180 ranitidine samples, including prescription and OTC products.[39] Samples were purchased from the marketplace, collected by FDA inspectors, or received in response to information requests. The dosage forms tested included tablets (75-150 milligrams (mg)), injectables (50 mg dose) and liquid syrups (75 mg dose).

Test results from industry and from samples obtained and tested by FDA showed that NDMA was consistently detected in ranitidine, and in many instances, it was detected above the ADI. On December 4, 2019, FDA announced to the public that the Agency had asked manufacturers to expand testing for NDMA to include all lots of the medication before releasing them for consumer use. The announcement reiterated that if test results for any lots showed NDMA above the level previously identified as the ADI, the manufacturer should recall the product if distributed, or not release the product to consumers and inform FDA. The Agency also communicated that it needed to further investigate how ranitidine behaves in the body, and that it had found some evidence of a link between the presence of nitrites and the formation of NDMA in the body if ranitidine was present. Since December, additional manufacturers have announced voluntary recalls of their products, which have been posted on the FDA Ranitidine webpage.

Today, April 1, 2020, FDA is sending letters to each firm marketing ranitidine requesting that they immediately initiate a voluntary withdrawal of all ranitidine drug product batches from the U.S. market.[40] Firms are also asked to cease further distribution. Firms should not resume

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[37] This level had previously been calculated as an interim acceptable limit for NDMA in ARBs. It is based on a calculated acceptable intake for NDMA in drugs based on methods described in the International Council for Harmonisation (ICH) guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (March 2018). See footnote 35 for more information on ARBs.

[38] See footnote 32, FDA update for November 1, 2019.

[39] The range of NDMA observed in ranitidine was 0.013 ppm to 2.97 ppm. FDA test results further showed that 46 samples from 12 DMF or ANDA holders had NDMA levels above the ADI of 0.32 ppm based on a 300 mg daily dose of ranitidine (which corresponds to the 96 ng ADI). Ranitidine manufacturers reported similar values for NDMA levels in their products as those observed by FDA.

[40] FDA sent Information Requests (IR) to applicants and pending applicants that market all dosage forms and strengths of ranitidine requesting a market withdrawal.

marketing of ranitidine finished drug products unless and until FDA approves a supplemental application that demonstrates adequate control over NDMA.[41] Applicants are instructed to send market withdrawal plans, including a product withdrawal timeline, to the designated division recall coordinator in the FDA Office of Regulatory Affairs (ORA) Division of Pharmaceutical Quality Operations (I-IV).

Additionally, FDA is announcing to consumers that they should stop taking over-the-counter ranitidine products, dispose of them properly and not purchase any more. Patients who are taking prescription ranitidine products should talk to their health care professional about other treatment options.

III. DISCUSSION

Your Petition specifically requests five actions based on testing conducted by Valisure. We are granting your Petition with respect to requests 1 (recall), 2 (investigate), and 3 (inform the public). We are denying requests 4 (additional instructions on waste disposal), and 5 (promulgate regulations and/or guidance). These decisions are discussed further below.

A. Recall, Investigate and Inform the Public

FDA's thinking on how to address NDMA impurities in ranitidine has evolved since it began the investigation in the summer 2019 to its decision today to request a market withdrawal of the drug product. FDA initially provided information that ranitidine drug products contained NDMA above acceptable limits to the public and manufacturers and distributors. The Agency supported applicants and manufacturers who voluntarily recalled ranitidine, and after obtaining sufficient scientific information on the levels of NDMA in ranitidine, we requested that manufacturers and distributors test their products and recall all ranitidine containing the impurity above acceptable levels.

FDA's investigation into NDMA impurities in ranitidine is ongoing. Recently, preliminary findings from stability testing raised concerns that NDMA levels in some ranitidine products stored at room temperature can increase with time to unacceptable levels, although in other products smaller changes were observed.[42] FDA's preliminary stability testing, using standard

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[41] The IR explains the data applicants must generate to demonstrate to the Agency that their ranitidine drug product meets applicable drug quality standards, specifically to ensure that adequate controls are in place to eliminate or limit NDMA levels in drug products. Companies that want to resume distribution of a ranitidine finished drug product in the U.S. market should provide acceptable stability data, including in-use conditions as described in the IR through labeled shelf life. FDA also recommends that applicants evaluate the cause(s) and extent of NDMA (and any other nitrosamine, if present as an impurity) formation over time, and optimize formulation and manufacturing controls and/or container/closure design to avert the formation of NDMA.

[42] For example, the Agency observed through its own laboratory testing that NDMA increased in the same batch of ranitidine over a period of 5 months at room temperature. The increase appears to be dependent on the formulation and how close the batch was to expiry.

accelerated stability conditions, demonstrated that elevated levels of NDMA were measured in all products after 2 weeks. Other testing conducted by FDA suggests that there is a correlation between NDMA levels and expiration date. Based on the data from NDMA testing in ranitidine drug products and drug substances, the preliminary results from FDA's stability testing, and other information available to the Agency, FDA is no longer confident that any ranitidine product will remain stable through its labeled expiration date.

Because of the recent data developed through the Agency's stability testing, and the continuing availability of ranitidine, FDA is requesting the market withdrawal of all ranitidine products, whether or not confirmatory testing has been conducted to demonstrate the presence of the NDMA impurity. FDA will continue to monitor the effectiveness of this market withdrawal and will take further action as appropriate.

FDA also agrees on the appropriateness of conducting examinations and investigations into the existence of NDMA impurities in ranitidine products. This information has been discussed above and published on the Agency's Ranitidine web page. Additionally, as noted above, FDA has been providing information to the public on a regular basis about the recalls and our investigation into NDMA impurities in ranitidine.

Although we are granting your Petition with respect to requesting manufacturers to remove all ranitidine products from the market, we did not rely on Valisure's testing results as presented in the Petition to reach this conclusion. We found that the test method you used in sampling ranitidine for NDMA was inappropriate and contributed to or caused the levels of NDMA to be artificially high.[43] In general, scientists ensure quality standards by testing a defined characteristic of a specific drug substance or specific drug product against established acceptance criteria for that characteristic.[44] To be considered an appropriate analytical test, FDA recommends that the tester provide data to demonstrate that a test procedure meets proper standards of accuracy, sensitivity, specificity and reproducibility, and is suitable for its intended purpose.[45] FDA also recommends that a quantitative analytical method be validated for its intended use through the demonstration of certain characteristics that are applicable for all types of tests. Typical validation characteristics are: specificity, linearity, accuracy, precision (repeatability, intermediate precision and reproducibility), range, and quantitation and detection limits.[46] Developing and validating a method requires the selection of appropriate analytical

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[43] The Petition indicates that Valisure used FDA's GC-MS headspace analysis method FY19-005-DPA for the determination of NDMA levels in ranitidine or other products. Even though this test method is appropriate for ARBs, this method is not suitable for ranitidine. This method utilizes a heat source, which leads to degradation of ranitidine and produces these artificially high levels of NDMA.

[44] See FDA guidance *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015) (guidance on Analytical Procedures) at 3.

[45] See Id. at 2-3. Applicants must submit appropriate analytical methods in their new or abbreviated drug application (21 CFR 314.50(d)(1); 314.94(a)(9)(i)).

[46] See guidance on Analytical Procedures at 7; see also ICH guidance for industry *Q2A on Text Validation of Analytical Procedures* (March 1995) and ICH guidance for industry *Q2B on Validation of Analytical Procedures: Methodology* (November 1996).

techniques, optimization of operation conditions, designing strategies for sample and standard preparations, and evaluating their stabilities. A method developed and validated for certain types of drugs or formulations is not appropriate for use on other drugs or formulations without separate validation.

To ensure that appropriate NDMA testing was used on all ranitidine products, FDA's Office of Testing and Research developed and validated two alternative liquid chromatography coupled with mass spectrometry (LC-MS) methods and posted them on the Agency's website.[47,48] Neither has the potential for "method-based" NDMA formation.[49] These two methods were validated for ranitidine drug substance and certain types of ranitidine drug products and have a limit of quantitation of 0.033 ppm of NDMA in drug products and a limit of detection of 0.011 ppm of NDMA. FDA's testing using these two orthogonal test methods (LC-HRMS and LC-MS/MS with multiple reaction monitoring), which are validated fit for purpose methods, have repeatedly indicated the presence of much lower levels of NDMA in ranitidine medicines than reported by Valisure.

The Petition makes several other arguments in support of its assertion that ranitidine drug products contain excessive levels of NDMA: the ranitidine molecule itself is unstable; ranitidine is unstable in humans, specifically in the stomach and intestines; the existence of a broadly expressed enzyme in the human body (DDAH-1) that facilitates NDMA formation; and an epidemiological study that implicated the drug class that includes ranitidine as being correlated to cancer. Because we have granted the Petition with respect to our market withdrawal action based on sufficient testing demonstrating NDMA in ranitidine and the lack of confidence that ranitidine will remain stable through expiration, FDA will not address these additional arguments regarding causation.

B. Current Instructions on Appropriate Disposal of Ranitidine are Sufficient

FDA does not agree that new provisions for the safe disposal of ranitidine need to be developed for the removal of ranitidine from the market given the potential for ranitidine to contain NDMA. FDA's web page on Disposal of Unused Medicine describes how to properly dispose of old,

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[47] One method, FY19-177-DPA-S utilizes high resolution mass spectrometry (LC-HRMS). See the FDA web page available at: https://www.fda.gov/media/130801/download.

[48] Another method, FY20-006-DPA-S, uses triple quadrupole mass spectrometry (LC-MS/MS), for the determination of NDMA in active pharmaceutical ingredients (API) and drug product. See FDA web page available at: https://www.fda.gov/media/131868/download. FDA released the second liquid chromatography-mass spectrometry (LC-MS) method to detect and quantify NDMA in ranitidine that uses a more widely available technology as an alternative. International regulators using similar LC-MS testing methods have also shown the presence of low levels of NDMA in ranitidine samples.

[49] In these two methods, NDMA is chromatographically separated from ranitidine API prior to ionization and detection by mass spectrometer, thus eliminating the risk of false NDMA results from ranitidine thermo-degradation. NDMA is selectively detected by its accurate mass or signature fragments in combination with LC retention time.

unused, unwanted or expired medicine.[50] We recently updated the drug disposal recommendations to highlight that the best way to dispose of most types of medicines (both prescription and over-the-counter) is to utilize a drug take-back site location or program immediately after the drug is no longer used. Additionally, FDA provides information to consumers on proper disposal of prescription and OTC medicines when take-back programs are not available. We note that this information is also being provided to consumers in the Agency's public statements on the removal of ranitidine from the market.

With respect to commercial disposal of unused or recalled ranitidine products, we expect that manufacturers and pharmacies will use appropriate disposal methods as identified by applicable federal, state or local jurisdictions. The Petition cites literature that shows a propensity for ranitidine to degrade to NDMA in conditions present in wastewater treatment facilities.[51] However, other literature indicates that the formation cannot be directly related to the decomposition of ranitidine and that there are many other conditions needed to form NDMA.[52] Based on the limited information provided in the Petition, it is not necessary for FDA to provide additional information or guidance on disposal of ranitidine drug products at this time.

C. Promulgation of Regulations and/or Guidance Requiring Independent Chemical Testing and Verification of Pharmaceuticals is Not Necessary at this Time

In the Petition, Valisure requests that FDA require independent chemical testing and verification of pharmaceuticals through regulation. We disagree that a regulation requiring or a guidance recommending independent testing is necessary. Applicants and manufacturers are required to ensure that their products meet all applicable standards for identity, strength, quality, purity and potency throughout the lifecycle of their drug products. See e.g. section 501 of the FD&C Act (21 U.S.C. 351). Existing regulations and guidance provide sufficient information for applicants and manufacturers, and FDA conducts sufficient oversight to ensure that quality drug products are released into the market.

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[50] FDA offers resources consumers can use to learn about the Agency's recommendation for proper disposal of unused medications: Disposal of Unused Medicines: What You Should Know, available at www.fda.gov/drugdisposal; Where and How to Dispose of Unused Medicines: https://www.fda.gov/consumers/consumer-updates/where-and-how-dispose-unused-medicines; Drug Disposal: Flush Potentially Dangerous Medicine: https://www.fda.gov/drugs/disposal-unused-medicines-what-you-should-know/drug-disposal-flush-potentially-dangerous-medicine#FlushList.

[51] Petition at 17.

[52] See Le Roux, J, et al, *NDMA Formation by Chloramination of Ranitidine: Kinetics and Mechanism*, 2012, Environ Sci Technol, Vol 46, 11095-11103; Chen, Z, and Valentine, RL, 2007, *Formation of N-nitrosodimethylamine (NDMA) from humic substances in natural water*, Environ Sci Technol, 41(17), 6059-6065; Krasner, SW, Mitch, W, et al., 2013, *Formation, precursors, control, and occurrence of nitrosamines in drinking water: A Review*, Water Research, 47:4433-4450.

FDA's CGMP regulations set minimum requirements for drug product manufacturers to use in adequately controlling their manufacturing operations.[53] This formal system of controls helps to prevent instances of contamination, mix-ups, deviations, failures, and errors and assures that drug products meet the quality standards identified in regulations. FDA guidance recommends that similar controls be exercised by active ingredient manufacturers before they release a batch of active ingredient for use by drug product manufacturers.[54] In addition, every establishment that is registered to engage in the manufacture, preparation, propagation, compounding or processing of a drug is subject to an inspection under section 704 of the FD&C Act. 21 U.S.C. 374) FDA's inspection programs provide additional oversight of manufacturing.[55]

FDA guidance provides recommendations to industry on how to assure quality standards are met by active ingredient manufacturers and drug product manufacturers.[56] If a new risk is identified, it is expected that the manufacturer will assess that risk and, as appropriate, take steps to address it, for example by updating control strategies. Manufacturers are the most familiar with their own processes, facilities and supply chains, and are therefore best placed to assess a risk. FDA evaluates data generated from any risk assessment and proposed changes by industry to address risk in accordance with the requirements in the statute and Agency regulations. While manufacturers may choose to use an independent third-party to perform certain tests if they have reason to be concerned about the reliability of their own results or to access sophisticated methods or equipment that may not otherwise be available to them, independent testing does not provide unique insight into risks and is therefore generally not warranted.

Similarly, FDA does not agree that guidance recommending independent chemical batch-level testing and verification of the chemical content of all pharmaceuticals is necessary. Because FDA does not agree that regulations should be implemented to require third-party independent testing of all pharmaceuticals, we also do not agree that a guidance on this topic should be

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[53] See generally 21 CFR parts 210 and 211. These regulations include requirements to establish strong quality management systems, obtaining appropriate quality components (ingredients), establishing robust laboratory controls and operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. Specifically, manufacturers must evaluate incoming component quality, test and/or examine the quality of in-process material, and test statistically representative samples of the drug product before each batch is released for consumer use.

[54] ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016 (Revision 1)); ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Questions and Answers* (April 2018).

[55] Section 510(h), 21 U.S.C. 360(h); see FDA Manual of Policies and Procedures 5014.1 "Understanding CDER's Risk-Based Site Selection Model" at 3 (September 26, 2018) (Goals of the surveillance inspection program are to ensure that sites consistently manufacture drug products of acceptable quality and minimize consumers' exposure to adulterated products).

[56] See e.g., ICH guidance for industry *Q8 (R2) Pharmaceutical Development* (November 2009, Rev. 2); ICH guidance for industry *Quality Risk Management* (June 2006) and ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009).

developed in the interim. We also note that implementation of such a system would be difficult. As a general principle, the degree of regulatory scrutiny over batch-level testing should be commensurate with the degree of risk, and an independent tester cannot evaluate the risk without sufficient knowledge of all manufacturing processes. Additionally, testing methods can only be developed with a target analyte in mind; testing of all possible chemical impurities or contaminants is not feasible. Beyond the problem of the volume of potential impurities to test, an independent third-party would need information concerning the formulation and manufacturing of a product to determine which chemical tests are appropriate, and to develop suitable methods for detection of impurities.

Because we do not agree that independent chemical testing and verification of pharmaceuticals are necessary, we deny this request. The Agency will reevaluate and update our policy as appropriate.

IV. CONCLUSION

For the foregoing reasons, FDA grants the Petition in part and denies the Petition in part.

Sincerely,

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research

TAB 4

FDA STATEMENT

FDA Statement on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings

For Immediate Release:

August 30, 2018

Statement From:

Commissioner of Food and Drugs - Food and Drug Administration
Scott Gottlieb M.D.
Director - Center for Drug Evaluation and Research
Janet Woodcock M.D.

Millions of Americans take medication daily to control their blood pressure. We recently found that some generic versions of one medication, valsartan, contain an impurity that doesn't meet FDA's safety standards. Valsartan is an angiotensin II receptor blocker (ARB) that treats high blood pressure and heart failure. The FDA currently has a major operation underway to investigate and address this troubling finding. This investigation is led by a dedicated task force of experts focused solely on this important work. Their mandate is to oversee the investigation and track new developments and information coming in from valsartan manufacturers. This multidisciplinary team of chemists, toxicologists, medical doctors, pharmacists, investigators, communication specialists, and analytical lab staff coordinates across the FDA, and acts on the newest available information.

As our investigation continues to identify the root cause of this impurity, we want to take the opportunity to describe to the public what we are doing to find the cause of the impurity, to prevent a recurrence of this episode and to protect patients who need this medication.

On June 19, a U.S. manufacturer of valsartan products, Prinston Pharmaceuticals Inc., contacted the FDA's Center for Drug Evaluation and Research (CDER) about its products containing valsartan active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceutical Co. (ZHP). Prinston informed CDER that they had

stopped making valsartan products because ZHP had detected an impurity in the API – a chemical known as N-nitrosodimethylamine (NDMA). NDMA is a probable cancer-causing chemical found in trace amounts in water and some foods. However, the levels of NDMA in ZHP's valsartan API – while still trace amounts – were unacceptable.

Although the risk to patients taking the affected products is extremely low, we take matters of pharmaceutical quality very seriously. We took immediate steps to address these findings.

Shortly after initiating our investigation, we learned that a foreign regulator was also reviewing medications containing valsartan API manufactured by ZHP and considering a recall. We have closely coordinated with the European Medicines Agency, European Directorate for the Quality of Medicines, Regulatory Operations and Regions Branch and Therapeutic Products Directorate of Health Canada, and the Pharmaceuticals and Medical Devices Agency in Japan since that time, sharing information about our investigation with them and other regulatory bodies and learning about their findings.

We recognized that we had to find answers to several important questions: How many U.S. valsartan products are affected? Where did the impurity come from? What are the potential health consequences of the impurity? How many patients are affected? How long have patients been exposed to NDMA? How do we ensure that patients and providers are informed so that health care is minimally disrupted? How do we prevent drug shortages? And could similar drugs also contain this impurity?

Our first priority was to inform patients and health care providers. To do this, we had to verify the information about ZHP's API to understand the risk to U.S. patients and the scope of APIs and products potentially affected by this impurity. We identified four manufacturers using valsartan API from ZHP for the U.S. market. We contacted them to ask if they knew about NDMA in their products and to recommend recalls of affected products. In addition to ZHP, we identified 13 other API manufacturers who supply more than 20 drug companies that make valsartan for the U.S. market. We made plans to determine if their products could also contain NDMA.

By July 13, we had the information we needed to issue a press release (/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity) stating that three companies had products containing NDMA and were voluntarily recalling them. One of the four

manufacturers we initially identified required further investigation, but has since voluntarily recalled (/drugs/drug-safety-and-availability/fda-updates-valsartan-recalls) its products.

However, we did not want patients taking valsartan to hear this news and abruptly stop their medications, possibly suffering serious medical issues, such as stroke. We needed to let patients know the specific products impacted by the recalls, so they could talk to their health care providers and get prescriptions for products that had not been recalled. We began posting frequent updates to our website, listing first the valsartan products affected by the recall (/media/115390/download), followed by a list of the hundreds of products not affected (/media/115393/download) at that time. We shared this information broadly across other communication channels known to reach consumers and health care providers, such as social media, newswires and email listservs. Because this is a continuing investigation, more manufacturers may discover that their valsartan products contain NDMA and take steps to voluntarily recall them. We encourage patients and prescribers to check these lists frequently for potential changes in the recall status of their medicine. We are continuing to update this information on a regular basis and update consumers over our social media platforms to ensure broad reach.

CDER toxicologists and chemists evaluated the risk to the public. On July 27, we shared (/drugs/drug-safety-and-availability/fda-updates-valsartan-recalls) what our scientists were able to estimate was the theoretical risk that the impurity could pose to patients. We estimated that if 8,000 people took the highest valsartan dose (320 mg) from NDMA-affected medicines daily for four years (the amount of time we believed the affected products had been on the U.S. market), there may be one additional case of cancer over the lifetimes of these 8,000 people beyond the average cancer rate among Americans. This estimate represented the highest possible level of NDMA exposure. It was a measure of the risk under the most extreme circumstances. Most patients who were exposed to the impurity through the use of valsartan received less exposure than this worst-case scenario.

In St. Louis, the FDA maintains the most advanced pharmaceutical laboratory of any regulatory agency in the world. As soon as we were aware of the NDMA impurity in certain valsartan drugs, we began collecting samples of all valsartan API and products marketed in the U.S. At the same time, our scientists began developing a test to detect and quantify NDMA in valsartan API. NDMA's properties make it difficult to find. To determine if valsartan products do contain this impurity, CDER's scientists have now developed the gas chromatography-mass spectrometry (GC/MS) headspace testing

method. We posted (/files/drugs/published/GC-MS-Headspace-Preliminary-Method-for-Detection-of-NDMA-in-Valsartan-Drug-Substance.pdf) this method to the web to help manufacturers and regulators detect NDMA in valsartan API and tablets.

Based on information provided regarding ZHP's manufacturing processes, we believed (but did not have proof) that the impurity resulted from changes that ZHP made to the manufacturing process for its API. We needed to identify the root cause of the problem and evaluate ZHP's explanation. After assessing information about ZHP's manufacturing processes and the changes ZHP made over time, we identified how its processes could have led to the presence of NDMA in their API.

Specifically, a combination of conditions, which include certain chemicals, processing conditions and production steps, could lead to formation of the NDMA impurity. We believe that these risks are introduced through a specific sequence of steps in the manufacturing process, where certain chemical reactions are needed to form the active ingredient. Before we undertook this analysis, neither regulators nor industry fully understood how NDMA could form during this process. We are still not 100 percent sure that this is the root cause of the problem. Full understanding will require correlation of multiple test results from valsartan APIs made by different processes with the various process steps used by different manufacturers or at different times. We need to determine how NDMA can be formed and why it is not separated from the API during purification.

Once we understand the way or ways that the NDMA impurity can occur as a by-product of the manufacturing process, we will make sure these conditions are evaluated in API synthetic processes so that, in the future, testing for this impurity would be required if there was a risk of NDMA formation.

NDMA is one chemical in a class called "genotoxic impurities". These chemicals are of special concern to global regulators because, unlike most impurities in drugs, they have the potential to cause harm at very low levels. The FDA has worked with international regulators to create standards for mitigating the risk of such impurities. We have robust policies and procedures in place to guard against these risks.

The FDA will continue to improve its procedures for guarding against these impurity risks. We will use the information that we learn from our investigation into valsartan to strengthen our oversight.

In March 2018, the FDA issued a guidance (/media/85885/download) for manufacturers that lays out risk assessements that manufacturers can use to evaluate the presence of genotoxic impurities. This is an internationally-harmonized guidance that both regulators and industry have agreed to. To implement the risk assessment for any genotoxic impurity, there has to be recognition that it can occur in the manufacture of the product. The guidance lays out the conditions under which these risks can occur, and the steps that manufacturers should take to test for these potential impurities.

Under the agency's longstanding policies, manufacturers are required to test for impurities that may be introduced or develop during their manufacturing processes. We review that information in product applications, including requests to change the manufacturing process. We employ robust teams of organic chemists, as part of our newly established Office of Pharmaceutical Quality, to review applications and referenced information to look for steps – and manufacturing changes – where these risks could be introduced.

The FDA also inspects manufacturing facilities across the world, and in routine current good manufacturing practices inspections, we can review a manufacturer's records regarding impurity testing. However, the review of records depends on appropriate tests to detect the impurity. Tests are selected based on assessments of what impurities may develop based on the manufacturing process. In other words, it needs to be recognized that the risk of an impurity can occur in order to know that it should be tested for.

Recognizing these risks is based on a deep understanding of the chemistry involved in drug manufacturing, and the theoretical risk that an impurity could be a by-product of an essential step used in the manufacture of an active ingredient. When these impurities are identified, there are ways to re-engineer manufacturing processes to find pathways that don't create these by-products. Because it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it. They would not have records that help identify this issue during an inspection. So this particular risk would not have been identified on an inspection. As we develop a better understanding of the root cause of NDMA formation, and develop a way to detect NDMA in valsartan or other ARBs, we can ensure that appropriate testing is performed in the future.

Based on our analyses of the manufacturing processes, we are now testing all the products in the ARB class to determine if they contain NDMA. In some cases, the steps in the synthesis of other ARBs can have similarities to the synthesis of valsartan. These tests will continue until we identify all products that may contain NDMA in the ARB class, and they are no longer available in the U.S. And our robust investigation continues, as do our efforts to mitigate these risks and prevent them from recurring.

The FDA has also inspected ZHP in response to this problem and the agency may re-inspect ZHP and inspect other manufacturers of valsartan API in the future. The FDA is coordinating with companies to take swift action to remove any products found with unacceptable amounts of NDMA from the U.S. market.

The initial recall has expanded to now include five manufacturers and other companies who repackage those products under a different name. More products may need to be recalled. At the same time, the FDA is working to make certain that patients have access to the treatment that they need. Currently, more than half of all valsartan products on the market are being recalled. But prescribers can find a similar replacement product within the same class to substitute for patients who require this medication.

We are also working very closely with global regulatory agencies, including the European Medicines Agency. The task force the FDA formed exchanges information with regulatory counterparts around the world including inspection findings, laboratory test method and results, and our scientific assessment of the cause of this problem and its impact on patients. While not every manufacturing site produces drugs for all countries, we believe sharing this information is vital to advancing our ongoing investigation. It enables us to address emerging issues quickly in a way that benefits U.S. patients. This includes monitoring actions other regulators are taking as part of their investigations. For example, international regulators have identified another API manufacturer, Zhejiang Tianyu Pharmaceutical Co., with NDMA in its valsartan API. But the FDA has confirmed that no valsartan products in the U.S. market use this API.

The FDA will continue to work closely with providers and patients to address health care needs.

The news of the recall caused a significant public response. Consumers were rightly concerned. CDER has a skilled group of pharmacists and nurses who manage a toll-free number (/about-fda/about-center-drug-evaluation-and-research/cder-division-

drug-information) (855-543-3784) and answer email inquiries (druginfo@fda.hhs.gov (mailto:druginfo@fda.hhs.gov)) from the public. Since the first news of a recall, the FDA has received more than 6,000 inquiries from patients, physicians, nurses, pharmacists and academicians. We take these inquiries very seriously, and we strive to answer all of them. The public wants to know how to get safe valsartan, what to tell their pharmacists, if they should stop taking their medications and how to calculate their risk for cancer if they have been taking affected valsartan for several years. It was these questions, in part, that prompted the FDA to conduct its analysis (/drugs/drug-safety-and-availability/fda-updates-valsartan-recalls) of the risk that NDMA posed.

As we develop a better understanding of the manufacturing process conditions that ZHP used that can cause the impurity, we will use that knowledge to inform assessments of product applications being submitted and currently reviewed by the FDA. We will disseminate that information to manufacturers of all drugs and to the scientific community and re-evaluate our existing guidance to manufacturers. In addition, the test method we developed for identifying NDMA helps us to prioritize assessments and inspections of manufacturing sites. The information we gather throughout this investigation will give us a better understanding of the manufacturing processes and will strengthen our efforts to keep the U.S. drug supply safe for patients.

In addition to our ongoing investigation, we will continue to update our website (/drugs/drug-safety-and-availability/fda-updates-valsartan-recalls), detailing lists of all recalled and non-recalled valsartan products as well as advice for patients and prescribers. We will also disclose our test results. This is a serious matter that is being managed closely by the FDA's leadership. As described above,we have a robust effort underway to evaluate these risks, led by a team of some of our most experienced scientists and clinicians. As we continue to investigate this episode, and develop new information, we will update the public regularly. We are committed to identifying the root causes of this impurity being found in valsartan, and taking steps to reduce the risk that similar episodes occur in the future.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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Inquiries

Media:

Jeremy Kahn (mailto:jeremy.kahn@fda.hhs.gov)

301-796-8671

Consumer:

888-INFO-FDA

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